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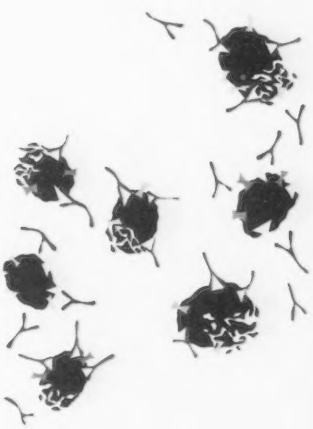

ON THE COVER
Artwork (cut Coloroid paper on paper) by New York artist Rachel Urkowitz (rachelurk@earthlink.net). Antibodies induced by vaccines (red) based on conserved bacterial antigens (yellow) cause the destruction of all pneumococcal variants (brown), whereas antibodies induced by nonconserved antigens (green) allow many variants to escape. Related article by Giefing et al.
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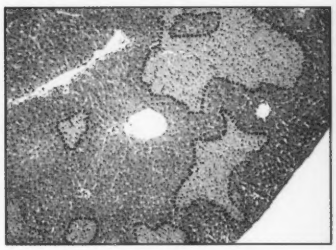

Mice that lack the osteopontin-suppressing proteoglycan Synd-4 are more susceptible to inflammation-induced liver injury (patches).
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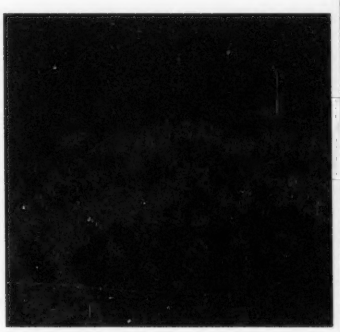

The transferrin receptor CD71 (blue) is overexpressed in the intestinal epithelium of patients with active celiac disease.
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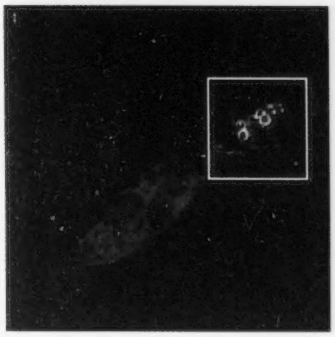

The binding of mannose-binding lectin (green) to TLR2 (red) in macrophage phagosomes boosts the innate immune response to *Staphylococcus* infection.
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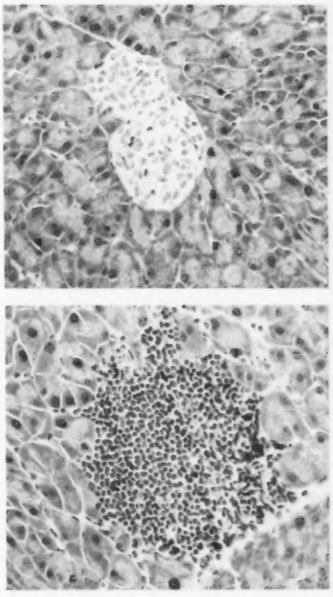

Diabetic mice treated with an interferon-γ–inducing antibody (top) have fewer inflamed pancreatic islets than do untreated diabetic mice (bottom).
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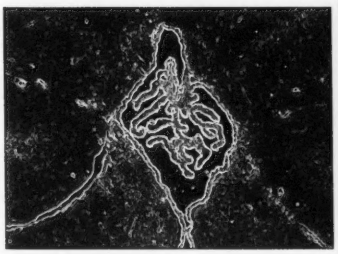

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Vascular endothelial growth factor keeps specialized epithelial cells that line brain cavities alive. These cells prevent fluid produced by brain cells that protrude into the cavity from leaking into the brain.
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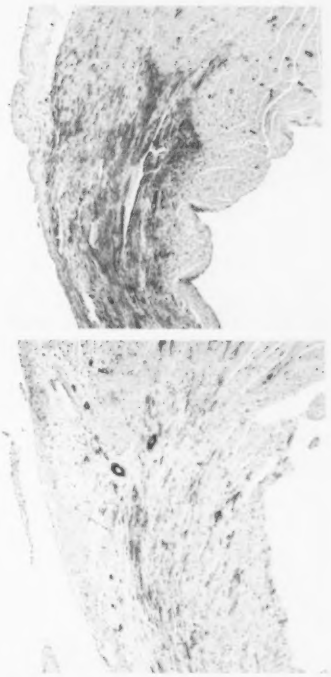

The recruitment of wound-healing fibroblasts (pink) into injured mouse hearts (top) is impaired in the absence of the extracellular matrix protein periostin (bottom).
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Fibroblasts expressing TNF receptors cause full-blown inflammation (dark patches) and arthritis in mice.
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451 **Homeostatic MyD88-dependent signals cause lethal inflammation in the absence of A20**
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Mice infected with murine cytomegalovirus (top) have fewer cerebellar folds in their brains than do normal mice (bottom).
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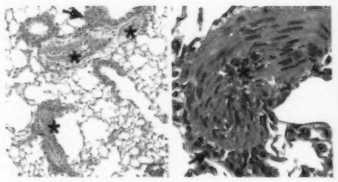

Lung arteries (asterisks) of mice that inhale *Aspergillus fumigatus* thicken over time (left to right).
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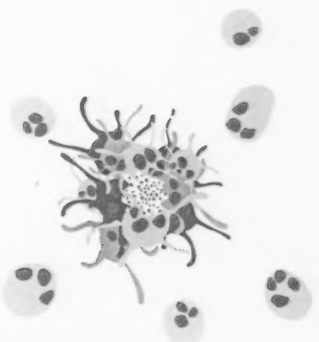

ON THE COVER
Artwork (cut Coloroid paper on paper) by New York artist Rachel Urkowitz (rachelurk@earthlink.net). Activated platelets secrete the memory chemical glutamate (red), which enhances clotting by increasing platelet activation and recruiting more platelets.
Related article by Morrell et al.
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565 **The AKT–mTOR axis regulates de novo differentiation of $CD4^+Foxp3^+$ cells**
Sokol Haxhinasto, Diane Mathis, and Christophe Benoist
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575 **Glutamate mediates platelet activation through the AMPA receptor**
Craig N. Morrell, Henry Sun, Masahiro Ikeda, Jean-Claude Beique, Anne Marie Swaim, Emily Mason, Tanika V. Martin, Laura E. Thompson, Oguz Gozen, David Ampagoomian, Rolf Sprengel, Jeffrey Rothstein, Nauder Faraday, Richard Huganir, and Charles J. Lowenstein
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585 **Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder**
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611 **Antagonism of FOG-1 and GATA factors in fate choice for the mast cell lineage**
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641 **Loss of the BH3-only protein Bmf impairs B cell homeostasis and accelerates γ irradiation–induced thymic lymphoma development**
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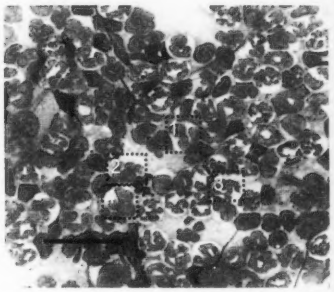
669 **A gammaherpesvirus-secreted activator of $V\beta4^+$ $CD8^+$ T cells regulates chronic infection and immunopathology**
Andrew G. Evans, Janice M. Moser, Laurie T. Krug, Veranika Pozharskaya, Ana L. Mora, and Samuel H. Speck



Hematopoeitic stem cells that are forced to express the microRNA miR-155 give rise to myeloid cells (numbered) rather than lymphoid cells.
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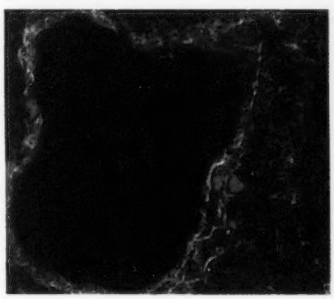

Flt 3 ligand (green) is expressed around thymic blood vessels (red) and attracts thymic progenitor cells from the bone marrow.
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685 **Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation**
Sébastien Conus, Remo Perozzo, Thomas Reinheckel, Christoph Peters, Leonardo Scapozza, Shida Yousefi, and Hans-Uwe Simon
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711 **Age-associated decline in T cell repertoire diversity leads to holes in the repertoire and impaired immunity to influenza virus**
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725 **CD94-NKG2A recognition of human leukocyte antigen (HLA)-E bound to an HLA class I leader sequence**
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739 **An antidote for *Staphylococcus aureus* pneumonia?**
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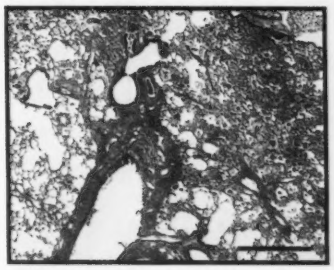

Mice that lack IFN-γ receptors develop fibrotic lung damage (blue) when infected with a gammaherpesvirus.
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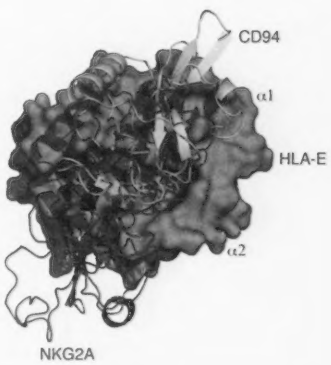

The HLA-E ligand (purple) interacts more with the CD94 subunit (green) of the NK receptor than with the NKG2A subunit (blue).
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OX40: a win–win path to tumor immunity
Flushing out neutrophils
A safer poxvirus vaccine
A matter of (V segment) choice
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744 Robert Ménard: Tailing malaria parasites to the red blood cell
Hema Bashyam

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747 The role of CTCF in regulating nuclear organization
Adam Williams and Richard A. Flavell

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759 12(S)-hydroxyheptadeca-5Z, 8E, 10E–trienoic acid is a natural ligand for leukotriene B_4 receptor 2
Toshiaki Okuno, Yoshiko Iizuka, Hiroshi Okazaki, Takehiko Yokomizo, Ryo Taguchi, and Takao Shimizu

767 Synthetic chemerin-derived peptides suppress inflammation through ChemR23
Jenna L. Cash, Rosie Hart, Andreas Russ, John P.C. Dixon, William H. Colledge, Joanne Doran, Alan G. Hendrick, Mark B.L. Carlton, and David R. Greaves

777 CXCR4 is required for the quiescence of primitive hematopoietic cells
Yuchun Nie, Yoon-Chi Han, and Yong-Rui Zou

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785 The insulator factor CTCF controls MHC class II gene expression and is required for the formation of long-distance chromatin interactions
Parimal Majumder, Jorge A. Gomez, Brian P. Chadwick, and Jeremy M. Boss
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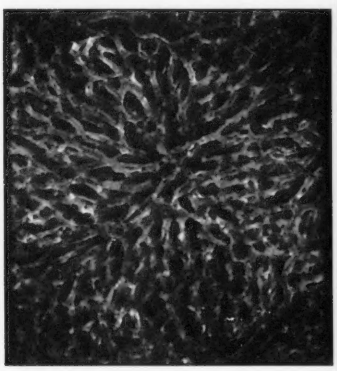

ON THE COVER
During sepsis, neutrophils (red) that enter the liver are trapped in capillaries (arrows) by a protein called SHAP (green). SHAP improves the binding affinity between CD44, a neutrophil surface molecule, and hyaluronan, an adhesion molecule on capillary walls.
Related article by McDonald et al.
See page 915

799 **Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category**
Dror Luger, Phyllis B. Silver, Jun Tang, Daniel Cua, Zoe Chen, Yoichiro Iwakura, Edward P. Bowman, Nicole M. Sgambellone, Chi-Chao Chan, and Rachel R. Caspi

811 **The Th17–ELR$^+$ CXC chemokine pathway is essential for the development of central nervous system autoimmune disease**
Thaddeus Carlson, Mark Kroenke, Praveen Rao, Thomas E. Lane, and Benjamin Segal

825 **OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection**
Silvia Piconese, Barbara Valzasina, and Mario P. Colombo
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841 **Polyomavirus BK with rearranged noncoding control region emerge in vivo in renal transplant patients and increase viral replication and cytopathology**
Rainer Gosert, Christine H. Rinaldo, Georg A. Funk, Adrian Egli, Emilio Ramos, Cinthia B. Drachenberg, and Hans H. Hirsch

853 **Phospholipase C-γ2 and Vav cooperate within signaling microclusters to propagate B cell spreading in response to membrane-bound antigen**
Michele Weber, Bebhinn Treanor, David Depoil, Hisaaki Shinohara, Naomi E. Harwood, Masaki Hikida, Tomohiro Kurosaki, and Facundo D. Batista

869 **Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells**
Mirjam Kool, Thomas Soullié, Menno van Nimwegen, Monique A.M. Willart, Femke Muskens, Steffen Jung, Henk C. Hoogsteden, Hamida Hammad, and Bart N. Lambrecht
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883 **Distinct cell-specific control of autoimmunity and infection by FcγRIIb**
Rebecca J. Brownlie, Kate E. Lawlor, Heather A. Niederer, Antony J. Cutler, Zou Xiang, Menna R. Clatworthy, R. Andres Floto, David R. Greaves, Paul A. Lyons, and Kenneth G.C. Smith

897 **IL-9– and mast cell–mediated intestinal permeability predisposes to oral antigen hypersensitivity**
Elizabeth E. Forbes, Katherine Groschwitz, J. Pablo Abonia, Eric B. Brandt, Elizabeth Cohen, Carine Blanchard, Richard Ahrens, Luqman Seidu, Andrew McKenzie, Richard Strait, Fred D. Finkelman, Paul S. Foster, Klaus I. Matthaei, Marc E. Rothenberg, and Simon P. Hogan

915 **Interaction of CD44 and hyaluronan is the dominant mechanism for neutrophil sequestration in inflamed liver sinusoids**
Braedon McDonald, Erin F. McAvoy, Florence Lam, Varinder Gill, Carol de la Motte, Rashmin C. Savani, and Paul Kubes
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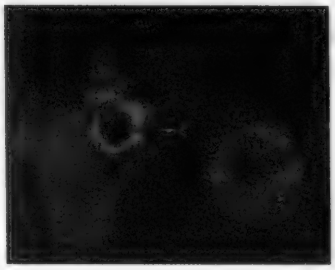

When leukocytes (red) need to pass through the endothelium, their plasma membrane (green) is enriched at the endothelial contact site.
See page 951

When arginine residues within fibrinogen are converted into citrulline residues posttranslationally, the modified protein becomes an autoantigen and induces joint swelling and arthritis in mice.
See page 967

929 **Gene placement and competition control T cell receptor γ variable region gene rearrangement**
Na Xiong, Li Zhang, Chulho Kang, and David H. Raulet
See news item on page 743

939 **A minimal binding footprint on CD1d-glycolipid is a basis for selection of the unique human NKT TCR**
Kwok S. Wun, Natalie A. Borg, Lars Kjer-Nielsen, Travis Beddoe, Ruide Koh, Stewart K. Richardson, Meena Thakur, Amy R. Howell, James P. Scott-Browne, Laurent Gapin, Dale I. Godfrey, James McCluskey, and Jamie Rossjohn

951 **Leukocyte transmigration requires kinesin-mediated microtubule-dependent membrane trafficking from the lateral border recycling compartment**
Zahra Mamdouh, Geri E. Kreitzer, and William A. Muller

967 **Arthritis induced by posttranslationally modified (citrullinated) fibrinogen in DR4-IE transgenic mice**
Jonathan A. Hill, David A. Bell, William Brintnell, David Yue, Bret Wehrli, Anthony M. Jevnikar, David M. Lee, Wolfgang Hueber, William H. Robinson, and Ewa Cairns

981 **The orthopoxvirus type I IFN binding protein is essential for virulence and an effective target for vaccination**
Ren-Huan Xu, Matthew Cohen, Yong Tang, Eric Lazear, J. Charles Whitbeck, Roselyn J. Eisenberg, Gary H. Cohen, and Luis J. Sigal
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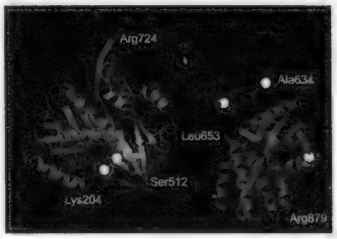
993 **Nonmuscle myosin heavy chain IIA mediates integrin LFA-1 de-adhesion during T lymphocyte migration**
Nicole A. Morin, Patrick W. Oakes, Young-Min Hyun, Dooyoung Lee, Y. Eugene Chin, Michael R. King, Timothy A. Springer, Motomu Shimaoka, Jay X. Tang, Jonathan S. Reichner, and Minsoo Kim



Mutated JAK1 residues (yellow) found in patients with acute lymphoblastic leukemia might increase JAK1 activity, which promotes cell proliferation.
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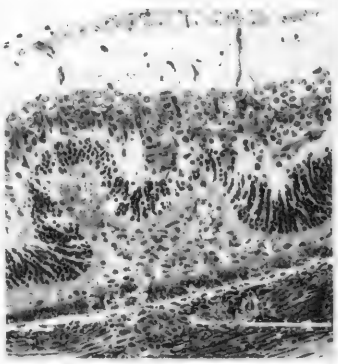

Severe eye inflammation develops in mice injected with CD4⁺ T cells that recognize an eye antigen and produce IFN-γ but not IL-17.
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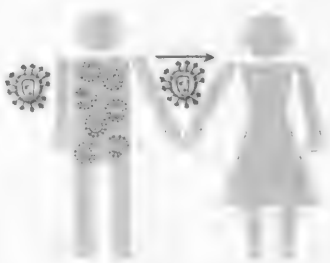

ON THE COVER
Artwork (cut Coloroid paper on paper) by New York artist Rachel Urkowitz (rachelurk@earthlink.net). Escape mutations (green) in HIV Gag (black) inflict a fitness cost on the virus and reduce its replicative ability in newly infected hosts.
Related article by Goepfert et al.
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EDITORIAL

996 You wrote it; you own it!
Emma Hill and Mike Rossner

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Spreading instead of growing
A trick presentation
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Dangers of restocking T cells
Hema Bashyam

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1000 Susan Allen: Confronting HIV in Africa
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1003 Crippling HIV one mutation at a time
Todd M. Allen and Marcus Altfeld

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1009 Transmission of HIV-1 Gag immune escape mutations is associated with reduced viral load in linked recipients
Paul A. Goepfert, Wendy Lumm, Paul Farmer, Philippa Matthews, Andrew Prendergast, Jonathan M. Carlson, Cynthia A. Derdeyn, Jianming Tang, Richard A. Kaslow, Anju Bansal, Karina Yusim, David Heckerman, Joseph Mulenga, Susan Allen, Philip J.R. Goulder, and Eric Hunter
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1019 IL-6–dependent spontaneous proliferation is required for the induction of colitogenic IL-17–producing $CD8^+$ T cells
Masaki Tajima, Daiko Wakita, Daisuke Noguchi, Kenji Chamoto, Zhang Yue, Kazunori Fugo, Harumichi Ishigame, Yoichiro Iwakura, Hidemitsu Kitamura, and Takashi Nishimura
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1029 During negative selection, Nur77 family proteins translocate to mitochondria where they associate with Bcl-2 and expose its proapoptotic BH3 domain
Jennifer Thompson and Astar Winoto

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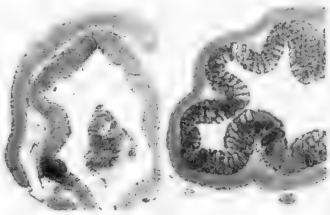
1037 Essential role of TNF receptor superfamily 25 (TNFRSF25) in the development of allergic lung inflammation
Lei Fang, Becky Adkins, Vadim Deyev, and Eckhard R. Podack

1049 **TL1A–DR3 interaction regulates Th17 cell function and Th17-mediated autoimmune disease**
Bhanu P. Pappu, Anna Borodovsky, Timothy S. Zheng, Xuexian Yang, Ping Wu, Xingwen Dong, Shawn Weng, Beth Browning, Martin L. Scott, Li Ma, Lihe Su, Qiang Tian, Pascal Schneider, Richard A. Flavell, Chen Dong, and Linda C. Burkly

1063 **Regulation of inflammatory responses by IL-17F**
Xuexian O. Yang, Seon Hee Chang, Heon Park, Roza Nurieva, Bhavin Shah, Luis Acero, Yi-Hong Wang, Kimberly S. Schluns, Russell R. Broaddus, Zhou Zhu, and Chen Dong



Mice that lack IL-17 (left) develop more severe colitis than mice that lack IL-17F (right).
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1077 **Native and aspirin-triggered lipoxins control innate immunity by inducing proteasomal degradation of TRAF6**
Fabiana S. Machado, Lísia Esper, Alexandra Dias, Rajat Madan, YuanYuan Gu, David Hildeman, Charles N. Serhan, Christopher L. Karp, and Júlio Aliberti
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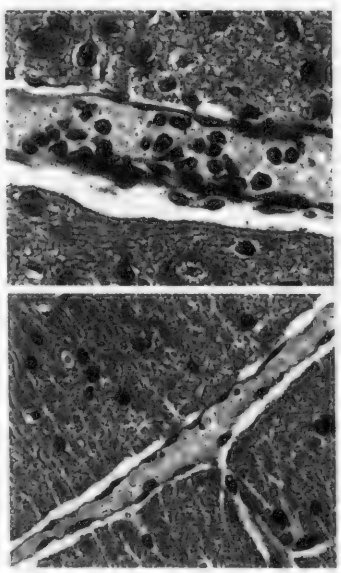
1087 **Essential role of Notch signaling in effector memory CD8$^+$ T cell–mediated airway hyperresponsiveness and inflammation**
Masakazu Okamoto, Katsuyuki Takeda, Anthony Joetham, Hiroshi Ohnishi, Hiroyuki Matsuda, Christina H. Swasey, Bradley J. Swanson, Koji Yasutomo, Azzeddine Dakhama, and Erwin W. Gelfand

1099 **A role for sex chromosome complement in the female bias in autoimmune disease**
Deborah L. Smith-Bouvier, Anagha A. Divekar, Manda Sasidhar, Sienmi Du, Seema K. Tiwari-Woodruff, Jennifer K. King, Arthur P. Arnold, Ram Raj Singh, and Rhonda R. Voskuhl

1109 **Bmi1 regulates memory CD4 T cell survival via repression of the *Noxa* gene**
Masakatsu Yamashita, Makoto Kuwahara, Akane Suzuki, Kiyoshi Hirahara, Ryo Shinnaksu, Hiroyuki Hosokawa, Akihiro Hasegawa, Shinichiro Motohashi, Atsushi Iwama, and Toshinori Nakayama

1121 **Virulent *Shigella flexneri* subverts the host innate immune response through manipulation of antimicrobial peptide gene expression**
Brice Sperandio, Béatrice Regnault, Jianhua Guo, Zhi Zhang, Samuel L. Stanley Jr., Philippe J. Sansonetti, and Thierry Pédron

1133 **C5 deficiency and C5a or C5aR blockade protects against cerebral malaria**
Samir N. Patel, Joanne Berghout, Fiona E. Lovegrove, Kodjo Ayi, Andrea Conroy, Lena Serghides, Gundula Min-oo, D. Channe Gowda, J. Vidya Sarma, Daniel Rittirsch, Peter A. Ward, W. Conrad Liles, Philippe Gros, and Kevin C. Kain



Mice that have the complement protein C5a (top) develop cerebral malaria due to inflammatory cell infiltration (blue), whereas mice that are C5a deficient (bottom) are resistant.
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1145 **Bone sialoprotein plays a functional role in bone formation and osteoclastogenesis**
Luc Malaval, Ndéyé Marième Wade-Guéye, Maya Boudiffa, Jia Fei, Ralph Zirngibl, Frieda Chen, Norbert Laroche, Jean-Paul Roux, Brigitte Burt-Pichat, François Duboeuf, Georges Boivin, Pierre Jurdic, Marie-Hélène Lafage-Proust, Joëlle Amédée, Laurence Vico, Janet Rossant, and Jane E. Aubin

1155 **The tumor suppressor semaphorin 3B triggers a prometastatic program mediated by interleukin 8 and the tumor microenvironment**
Charlotte Rolny, Lorena Capparuccia, Andrea Casazza, Massimiliano Mazzone, Antonella Vallario, Alessandro Cignetti, Enzo Medico, Peter Carmeliet, Paolo M. Comoglio, and Luca Tamagnone
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1173 **T cell receptor–instructed αβ versus γδ lineage commitment revealed by single-cell analysis**
Taras Kreslavsky, Annette I. Garbe, Andreas Krueger, and Harald von Boehmer

1187 **The stream of precursors that colonizes the thymus proceeds selectively through the early T lineage precursor stage of T cell development**
Claudia Benz, Vera C. Martins, Freddy Radtke, and Conrad C. Bleul

1201 **MR1 uses an endocytic pathway to activate mucosal-associated invariant T cells**
Shouxiong Huang, Susan Gilfillan, Sojung Kim, Bruce Thompson, Xiaoli Wang, Andrea J. Sant, Daved H. Fremont, Olivier Lantz, and Ted H. Hansen
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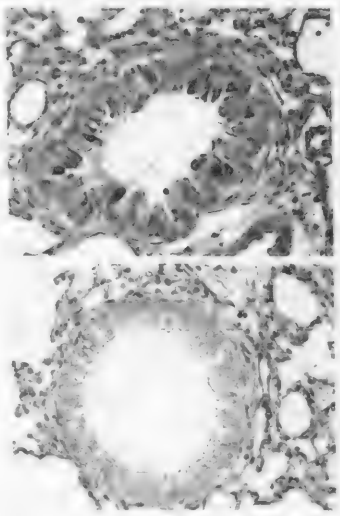
1213 **IL-15Rα chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation**
Erwan Mortier, Tammy Woo, Rommel Advincula, Sara Gozalo, and Averil Ma

1227 **ATF4 is an oxidative stress–inducible, prodeath transcription factor in neurons in vitro and in vivo**
Philipp S. Lange, Juan C. Chavez, John T. Pinto, Giovanni Coppola, Chiao-Wang Sun, Tim M. Townes, Daniel H. Geschwind, and Rajiv R. Ratan

CORRECTIONS

1243 **Phospholipase C-γ2 and Vav cooperate within signaling microclusters to propagate B cell spreading in response to membrane-bound antigen**
Michele Weber, Bebhinn Treanor, David Depoil, Hisaaki Shinohara, Naomi E. Harwood, Masaki Hikida, Tomohiro Kurosaki, and Facundo D. Batista



Lung inflammation (top) that leads to asthma is blocked when mice are treated with an anti-TNF receptor 25 antibody (bottom).
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Mice lacking sialoprotein have shorter bones (right).
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Balanced T cell subsets for good health
Retraining macrophages to kill tumors
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Endothelial cells instigate sepsis
Hema Bashyam

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1248 Vamsi Mootha: Taking an inventory of mitochondria
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1251 Sheepish B cells: evidence for antigen-independent antibody diversification in humans and mice
David Tarlinton

1255 IKKβ/NF-κB and the miscreant macrophage
Anjuli M. Timmer and Victor Nizet

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1261 "Re-educating" tumor-associated macrophages by targeting NF-κB
Thorsten Hagemann, Toby Lawrence, Iain McNeish, Kellie A. Charles, Hagen Kulbe, Richard G. Thompson, Stephen C. Robinson, and Frances R. Balkwill
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1269 An antiinflammatory role for IKKβ through the inhibition of "classical" macrophage activation
Carol Ho Yan Fong, Magali Bebien, Arnaud Didierlaurent, Ruth Nebauer, Tracy Hussell, David Broide, Michael Karin, and Toby Lawrence
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1277 Toll-like receptor 9 inhibition reduces mortality in polymicrobial sepsis
George Plitas, Bryan M. Burt, Hoang M. Nguyen, Zubin M. Bamboat, and Ronald P. DeMatteo

1285 Strain-specific requirement for eosinophils in the recruitment of T cells to the lung during the development of allergic asthma
Elizabeth Rose Walsh, Nisebita Sahu, Jennifer Kearley, Ebony Benjamin, Boo Hyon Kang, Alison Humbles, and Avery August

1293 Follicular dendritic cells control engulfment of apoptotic bodies by secreting Mfge8
Jan Kranich, Nike Julia Krautler, Ernst Heinen, Magdalini Polymenidou, Claire Bridel, Anita Schildknecht, Christoph Huber, Marie H. Kosco-Vilbois, Rolf Zinkernagel, Gino Miele, and Adriano Aguzzi

ON THE COVER
Image (provided by Pietro M. Motta and Tomonori Naguro / Photo Researchers, Inc) shows a colored high resolution scanning electron micrograph of two lysosomes in a pancreatic acinar cell. When the lysosomal membrane protein TRP-ML1 is mutated, the lysosome internalizes endosomal lipid cargo but fails to digest it, causing a lipid pile-up (top). Related story by Miedel et al.
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ARTICLES

1303 **Divergent roles of endothelial NF-κB in multiple organ injury and bacterial clearance in mouse models of sepsis**
Xiaobing Ye, Jianqiang Ding, Xiaozhou Zhou, Guoqian Chen, and Shu Fang Liu
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1317 **Constitutive CD40 signaling in B cells selectively activates the noncanonical NF-κB pathway and promotes lymphomagenesis**
Cornelia Hömig-Hölzel, Caroline Hojer, Julia Rastelli, Stefano Casola, Lothar J. Strobl, Werner Müller, Leticia Quintanilla-Martinez, Andreas Gewies, Jürgen Ruland, Klaus Rajewsky, and Ursula Zimber-Strobl

1331 **Somatic diversification in the absence of antigen-driven responses is the hallmark of the IgM$^+$IgD$^+$CD27$^+$ B cell repertoire in infants**
Sandra Weller, Maria Mamani-Matsuda, Capucine Picard, Corinne Cordier, Damiana Lecoeuche, Frédéric Gauthier, Jean-Claude Weill, and Claude-Agnès Reynaud
See Commentary on page 1251

1343 **A unique B2 B cell subset in the intestine**
Yasuyo Shimomura, Atsuhiro Ogawa, Mayumi Kawada, Ken Sugimoto, Emiko Mizoguchi, Hai-Ning Shi, Shiv Pillai, Atul K. Bhan, and Atsushi Mizoguchi
See Commentary on page 1251

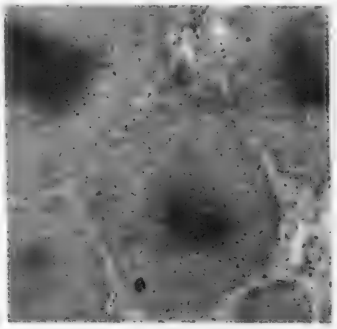
1357 **Proteasomal degradation restricts the nuclear lifespan of AID**
Said Aoufouchi, Ahmad Faili, Carole Zober, Orietta D'Orlando, Sandra Weller, Jean-Claude Weill, and Claude-Agnès Reynaud

1369 **Development and characterization of IL-21–producing CD4$^+$ T cells**
Akira Suto, Daisuke Kashiwakuma, Shin-ichiro Kagami, Koichi Hirose, Norihiko Watanabe, Kotaro Yokote, Yasushi Saito, Toshinori Nakayama, Michael J. Grusby, Itsuo Iwamoto, and Hiroshi Nakajima

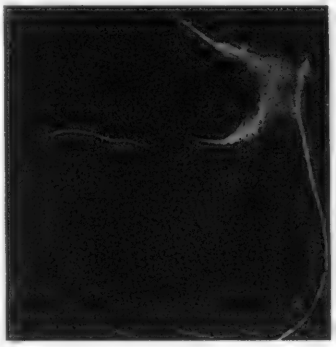
1381 **In vivo equilibrium of proinflammatory IL-17$^+$ and regulatory IL-10$^+$ Foxp3$^+$ RORγt$^+$ T cells**
Matthias Lochner, Lucie Peduto, Marie Cherrier, Shinichiro Sawa, Francina Langa, Rosa Varona, Dieter Riethmacher, Mustapha Si-Tahar, James P. Di Santo, and Gérard Eberl
See news item on page 1246

1395 **Control of hematopoietic stem cell quiescence by the E3 ubiquitin ligase Fbw7**
Benjamin J. Thompson, Vladimir Jankovic, Jie Gao, Silvia Buonamici, Alan Vest, Jennifer May Lee, Jiri Zavadil, Stephen D. Nimer, and Iannis Aifantis

1409 **Breaking tolerance to the natural human liver autoantigen cytochrome P450 2D6 by virus infection**
Martin Holdener, Edith Hintermann, Monika Bayer, Antje Rhode, Evelyn Rodrigo, Gudrun Hintereder, Eric F. Johnson, Frank J. Gonzalez, Josef Pfeilschifter, Michael P. Manns, Matthias von G. Herrath, and Urs Christen



Mice whose B cells express a constitutively active CD40 receptor have abnormally large lymph node follicles (brown) and develop lymphoma.
See page 1317



Liver infection with an autoantigen-expressing virus breaks tolerance and triggers excessive collagen deposition (green) and other autoimmune damage.
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1423 **A generic mechanism in *Neisseria meningitidis* for enhanced resistance against bactericidal antibodies**
Maria Jose Uria, Qian Zhang, Yanwen Li, Angel Chan, Rachel M. Exley, Bridget Gollan, Hannah Chan, Ian Feavers, Andy Yarwood, Raquel Abad, Ray Borrow, Roland A. Fleck, Barbara Mulloy, Julio A. Vazquez, and Christoph M. Tang

1435 **Sialyltransferase ST3Gal-IV controls CXCR2-mediated firm leukocyte arrest during inflammation**
David Frommhold, Andreas Ludwig, M. Gabriele Bixel, Alexander Zarbock, Inna Babushkina, Melitta Weissinger, Sandra Cauwenberghs, Lesley G. Ellies, Jamey D. Marth, Annette G. Beck-Sickinger, Michael Sixt, Bärbel Lange-Sperandio, Alma Zernecke, Ernst Brandt, Christian Weber, Dietmar Vestweber, Klaus Ley, and Markus Sperandio

1447 **Differential regulation of interleukin 12 and interleukin 23 production in human dendritic cells**
Franca Gerosa, Barbara Baldani-Guerra, Lyudmila A. Lyakh, Giovanna Batoni, Semih Esin, Robin T. Winkler-Pickett, Maria Rita Consolaro, Mario De Marchi, Daniela Giachino, Angela Robbiano, Marco Astegiano, Angela Sambataro, Robert A. Kastelein, Giuseppe Carra, and Giorgio Trinchieri

1463 **A crucial role for HVEM and BTLA in preventing intestinal inflammation**
Marcos W. Steinberg, Olga Turovskaya, Raziya B. Shaikh, Gisen Kim, Declan F. McCole, Klaus Pfeffer, Kenneth M. Murphy, Carl F. Ware, and Mitchell Kronenberg

1477 **Membrane traffic and turnover in TRP-ML1–deficient cells: a revised model for mucolipidosis type IV pathogenesis**
Mark T. Miedel, Youssef Rbaibi, Christopher J. Guerriero, Grace Colletti, Kelly M. Weixel, Ora A. Weisz, and Kirill Kiselyov
See news item on page 1247

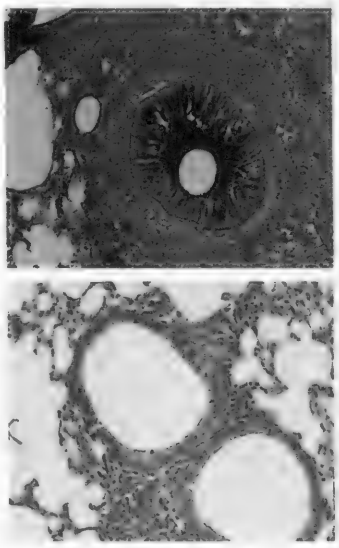
1491 **Acetylation of mitogen-activated protein kinase phosphatase-1 inhibits Toll-like receptor signaling**
Wangsen Cao, Clare Bao, Elizaveta Padalko, and Charles J. Lowenstein

CORRECTIONS

1505 **OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection**
Silvia Piconese, Barbara Valzasina, and Mario P. Colombo

1507 **Regulation of the germinal center gene program by interferon (IFN) regulatory factor 8/IFN consensus sequence-binding protein**
Chang Hoon Lee, Mark Melchers, Hongsheng Wang, Ted A. Torrey, Rebecca Slota, Chen-Feng Qi, Ji Young Kim, Patricia Lugar, Hee Jeong Kong, Lila Farrington, Boris van der Zouwen, Jeff X. Zhou, Vassilios Lougaris, Peter E. Lipsky, Amrie C. Grammer, and Herbert C. Morse, III

1509 **Divergent roles of endothelial NF-κB in multiple organ injury and bacterial clearance in mouse models of sepsis**
Xiaobing Ye, Jianqiang Ding, Xiaozhou Zhou, Guoqian Chen, and Shu Fang Liu



Lack of eosonophils triggers airway constriction and asthma in BALB/c (top), but not in C57BL/6, mice (bottom).
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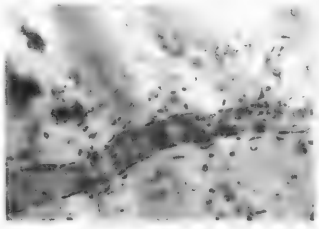

Leukocytes fail to stick to inflamed blood vessels in mice whose chemokine receptors lack post-translational sialic acid modifications (top).
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Timing tolerance to cancer
Why less is worse for lupus
Tumor suppressor fends off lung fibrosis
Two paths lead to MS
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1529 Polymers and inflammation: disease mechanisms of the serpinopathies
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1535 IL-12– and IL-23–modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition
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1543 Mutations in *STAT3* and *IL12RB1* impair the development of human IL-17–producing T cells
Ludovic de Beaucoudrey, Anne Puel, Orchidée Filipe-Santos, Aurélie Cobat, Pegah Ghandil, Maya Chrabieh, Jacqueline Feinberg, Horst von Bernuth, Arina Samarina, Lucile Jannière, Claire Fieschi, Jean-Louis Stéphan, Catherine Boileau, Stanislas Lyonnet, Guillaume Jondeau, Valérie Cormier-Daire, Martine Le Merrer, Cyrille Hoarau, Yvon Lebranchu, Olivier Lortholary, Marie-Olivia Chandesris, François Tron, Eleonora Gambineri, Lucia Bianchi, Carlos Rodriguez-Gallego, Simona E. Zitnik, Julia Vasconcelos, Margarida Guedes, Artur Bonito Vitor, Laszlo Marodi, Helen Chapel, Brenda Reid, Chaim Roifman, David Nadal, Janine Reichenbach, Isabel Caragol, Ben-Zion Garty, Figen Dogu, Yildiz Camcioglu, Sanyie Gülle, Ozden Sanal, Alain Fischer, Laurent Abel, Birgitta Stockinger, Capucine Picard, and Jean-Laurent Casanova

1551 Deficiency of Th17 cells in hyper IgE syndrome due to mutations in *STAT3*
Cindy S. Ma, Gary Y.J. Chew, Nicholas Simpson, Archana Priyadarshi, Melanie Wong, Bodo Grimbacher, David A. Fulcher, Stuart G. Tangye, and Matthew C. Cook

ON THE COVER
Watercolor by New York artist Emilie Clark (emilie@emilieclark.com). Image depicts lung damage seen in idiopathic pulmonary fibrosis (IPF). A defect in the phosphatase PTEN results in overactive lung fibroblasts and collagen accumulation in patients with IPF.
Related story by Xia et al.
See page 1659

1559 **Foxp3⁺ regulatory T cells maintain immune homeostasis in the skin**
Jan C. Dudda, Nikole Perdue, Eva Bachtanian, and Daniel J. Campbell

1567 **Sγ3 switch sequences function in place of endogenous Sγ1 to mediate antibody class switching**
Ali A. Zarrin, Peter H. Goff, Kate Senger, and Frederick W. Alt

1573 **Copy number of *FCGR3B*, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake**
Lisa C. Willcocks, Paul A. Lyons, Menna R. Clatworthy, James I. Robinson, Wanling Yang, Stephen A. Newland, Vincent Plagnol, Naomi N. McGovern, Alison M. Condliffe, Edwin R. Chilvers, Dwomoa Adu, Elaine C. Jolly, Richard Watts, Yu Lung Lau, Ann W. Morgan, Gerard Nash, and Kenneth G.C. Smith
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1583 **The calcium sensor STIM1 is an essential mediator of arterial thrombosis and ischemic brain infarction**
David Varga-Szabo, Attila Braun, Christoph Kleinschnitz, Markus Bender, Irina Pleines, Mirko Pham, Thomas Renné, Guido Stoll, and Bernhard Nieswandt
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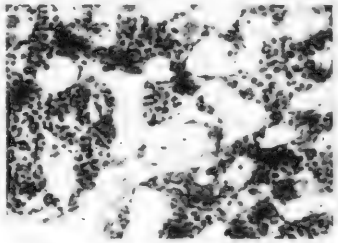
1593 **CNI-1493 inhibits Aβ production, plaque formation, and cognitive deterioration in an animal model of Alzheimer's disease**
Michael Bacher, Richard Dodel, Bayan Aljabari, Kathy Keyvani, Philippe Marambaud, Rakez Kayed, Charles Glabe, Nicole Goertz, Anne Hoppmann, Norbert Sachser, Jens Klotsche, Susanne Schnell, Lars Lewejohann, and Yousef Al-Abed



Apoptotic stem cells (red) accumulate in the bone marrow of mice lacking the kinase TAK1.
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ARTICLES

1601 **Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid–inducible gene-I and melanoma differentiation–associated gene 5**
Hiroki Kato, Osamu Takeuchi, Eriko Mikamo-Satoh, Reiko Hirai, Tomoji Kawai, Kazufumi Matsushita, Akane Hiiragi, Terence S. Dermody, Takashi Fujita, and Shizuo Akira
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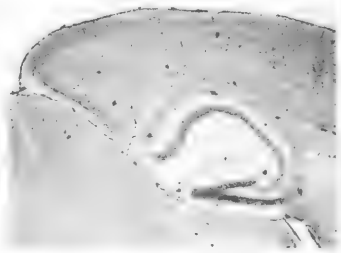
1611 **TAK1 is required for the survival of hematopoietic cells and hepatocytes in mice**
Minghui Tang, Xudong Wei, Yinshi Guo, Peter Breslin, Shubin Zhang, Shanshan Zhang, Wei Wei, Zhenbiao Xia, Manuel Diaz, Shizuo Akira, and Jiwang Zhang

1621 **Clearance of influenza virus from the lung depends on migratory langerin⁺CD11b⁻ but not plasmacytoid dendritic cells**
Corine H. GeurtsvanKessel, Monique A.M. Willart, Leonie S. van Rijt, Femke Muskens, Mirjam Kool, Chantal Baas, Kris Thielemans, Clare Bennett, Björn E. Clausen, Henk C. Hoogsteden, Albert D.M.E. Osterhaus, Guus F. Rimmelzwaan, and Bart N. Lambrecht



The antiinflammatory compound CNI-1493 reduces β-amyloid plaque (spots) formation in mice.
See page 1593

1635 **Protective influenza-specific CD8 T cell responses require interactions with dendritic cells in the lungs**
Jodi McGill, Nico Van Rooijen, and Kevin L. Legge

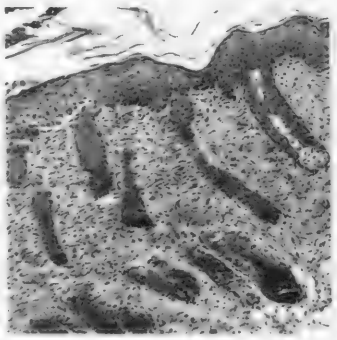
1647 **An MHC class Ib–restricted CD8 T cell response confers antiviral immunity**
Phillip A. Swanson II, Christopher D. Pack, Annette Hadley, Chyung-Ru Wang, Iwona Stroynowski, Peter E. Jensen, and Aron E. Lukacher

1659 **Pathological integrin signaling enhances proliferation of primary lung fibroblasts from patients with idiopathic pulmonary fibrosis**
Hong Xia, Deanna Diebold, Richard Nho, David Perlman, Jill Kleidon, Judy Kahm, Svetlana Avdulov, Mark Peterson, John Nerva, Peter Bitterman, and Craig Henke
See news item on page 1513

1673 **Tumor angiogenesis and progression are enhanced by Sema4D produced by tumor-associated macrophages**
Jose Rafael Sierra, Simona Corso, Luisa Caione, Virna Cepero, Paolo Conrotto, Alessandro Cignetti, Wanda Piacibello, Atsushi Kumanogoh, Hitoshi Kikutani, Paolo Maria Comoglio, Luca Tamagnone, and Silvia Giordano

1687 **Immunogenicity of premalignant lesions is the primary cause of general cytotoxic T lymphocyte unresponsiveness**
Gerald Willimsky, Melinda Czéh, Christoph Loddenkemper, Johanna Gellermann, Karin Schmidt, Peter Wust, Harald Stein, and Thomas Blankenstein
See news item on page 1512

1701 **Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets**
Claude Sportès, Frances T. Hakim, Sarfraz A. Memon, Hua Zhang, Kevin S. Chua, Margaret R. Brown, Thomas A. Fleisher, Michael C. Krumlauf, Rebecca R. Babb, Catherine K. Chow, Terry J. Fry, Julie Engels, Renaud Buffet, Michel Morre, Robert J. Amato, David J. Venzon, Robert Korngold, Andrew Pecora, Ronald E. Gress, and Crystal L. Mackall



Regulatory T cells prevent the development of spontaneous skin lesions (purple) in mice.
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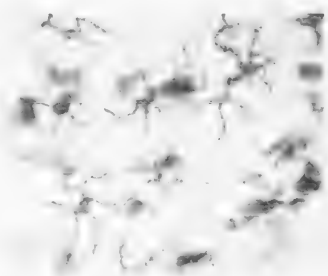

Different subsets of lung dendritic cells (orange) perform distinct functions in flu-infected mice.
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1716 Triple punch against trypanosomes
HIV switches to escape
Selective signaling
*Twist*ed control
Cranking out healthy platelets
Hema Bashyam

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1718 Facundo Batista: watching B cells spread and grab antigens
Hema Bashyam

BRIEF DEFINITIVE REPORTS

1721 Distinct roles of apolipoprotein components within the trypanosome lytic factor complex revealed in a novel transgenic mouse model
Maria Pilar Molina-Portela, Marie Samanovic, and Jayne Raper
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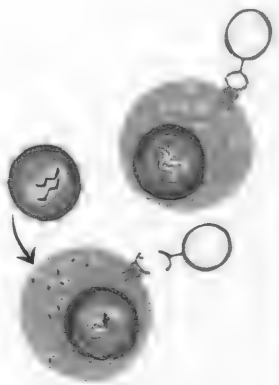
1729 Complementation of a pathogenic *IFNGR2* misfolding mutation with modifiers of N-glycosylation
Guillaume Vogt, Jacinta Bustamante, Ariane Chapgier, Jacqueline Feinberg, Stephanie Boisson Dupuis, Capucine Picard, Nizar Mahlaoui, Laure Gineau, Alexandre Alcaïs, Christophe Lamaze, Jennifer M. Puck, Geneviève de Saint Basile, Claudia Djambas Khayat, Raymond Mikhael, and Jean-Laurent Casanova

1739 Protease-activated receptor 1 activation is necessary for monocyte chemoattractant protein 1–dependent leukocyte recruitment in vivo
Daxin Chen, Adam Carpenter, Joel Abrahams, Rachel C. Chambers, Robert I. Lechler, John H. McVey, and Anthony Dorling

1747 TLR4-induced IFN-γ production increases TLR2 sensitivity and drives Gram-negative sepsis in mice
Stephan Spiller, Greg Elson, Ruth Ferstl, Stefan Dreher, Thomas Mueller, Marina Freudenberg, Bruno Daubeuf, Hermann Wagner, and Carsten J. Kirschning

1755 IL-17 produced by Paneth cells drives TNF-induced shock
Nozomi Takahashi, Ineke Vanlaere, Riet de Rycke, Anje Cauwels, Leo A.B. Joosten, Erik Lubberts, Wim B. van den Berg, and Claude Libert

1763 EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN-γ and IL-2
Jan D. Lünemann, Ilijas Jelčić, Susanne Roberts, Andreas Lutterotti, Björn Tackenberg, Roland Martin, and Christian Münz

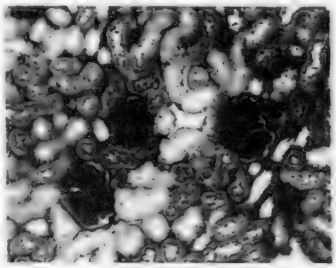


ON THE COVER
Artwork (cut Coloroid paper on paper) by New York artist Rachel Urkowitz (rachelurk@earthlink.net). Image depicts how recombination between different HIV strains allows the virus to escape from HIV-specific T cells (green). Recombination events that occur at T cell–targeted regions (yellow) produce new strains that are no longer recognized by T cells. Related article by Streeck et al.
See page 1789

1789 **Immune-driven recombination and loss of control after HIV superinfection**
Hendrik Streeck, Bin Li, Art F.Y. Poon, Arne Schneidewind, Adrianne D. Gladden, Karen A. Power, Demetre Daskalakis, Suzane Bazner, Rosario Zuniga, Christian Brander, Eric S. Rosenberg, Simon D.W. Frost, Marcus Altfeld, and Todd M. Allen
See news item on page 1716

1797 **Evidence for HIV-associated B cell exhaustion in a dysfunctional memory B cell compartment in HIV-infected viremic individuals**
Susan Moir, Jason Ho, Angela Malaspina, Wei Wang, Angela C. DiPoto, Marie A. O'Shea, Gregg Roby, Shyam Kottilil, James Arthos, Michael A. Proschan, Tae-Wook Chun, and Anthony S. Fauci

1929 **Transcriptional role of p53 in interferon-mediated antiviral immunity**
César Muñoz-Fontela, Salvador Macip, Luis Martínez-Sobrido, Lauren Brown, Joseph Ashour, Adolfo García-Sastre, Sam W. Lee, and Stuart A. Aaronson



Renal tissues in mice lacking the Toll-like receptor Sigrr are coated with disease-triggering autoantibodies (black).
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ARTICLES

1775 **Requirements of SLP76 tyrosines in ITAM and integrin receptor signaling and in platelet function in vivo**
Natalie A. Bezman, Lurong Lian, Charles S. Abrams, Lawrence F. Brass, Mark L. Kahn, Martha S. Jordan, and Gary A. Koretzky
See news item on page 1716

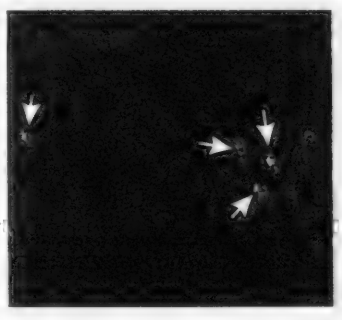
1807 **Discriminating gene expression profiles of memory B cell subpopulations**
Götz R.A. Ehrhardt, Atsushi Hijikata, Hiroshi Kitamura, Osamu Ohara, Ji-Yang Wang, and Max D. Cooper

1819 **Tolerance of NK cells encountering their viral ligand during development**
Joseph C. Sun and Lewis L. Lanier

1829 **Continuous engagement of a self-specific activation receptor induces NK cell tolerance**
Sandeep K. Tripathy, Peter A. Keyel, Liping Yang, Jeanette T. Pingel, Tammy P. Cheng, Achim Schneeberger, and Wayne M. Yokoyama

1843 **Transvection mediated by the translocated cyclin D1 locus in mantle cell lymphoma**
Hui Liu, Jing Huang, Jin Wang, Shuguang Jiang, Alexis S. Bailey, Devorah C. Goldman, Markus Welcker, Victoria Bedell, Marilyn L. Slovak, Bruce Clurman, Mathew Thayer, William H. Fleming, and Elliot Epner

1859 **Avidity maturation of memory CD8 T cells is limited by self-antigen expression**
Michael J. Turner, Evan R. Jellison, Elizabeth G. Lingenheld, Lynn Puddington, and Leo Lefrançois



Th17 cells arise from $CD4^+$ T cells that express CD161 marker (arrows).
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1869 **A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease**
Maria Björkqvist, Edward J. Wild, Jenny Thiele, Aurelio Silvestroni, Ralph Andre, Nayana Lahiri, Elsa Raibon, Richard V. Lee, Caroline L. Benn, Denis Soulet, Anna Magnusson, Ben Woodman, Christian Landles, Mahmoud A. Pouladi, Michael R. Hayden, Azadeh Khalili-Shirazi, Mark W. Lowdell, Patrik Brundin, Gillian P. Bates, Blair R. Leavitt, Thomas Möller, and Sarah J. Tabrizi

1879 **Tir8/Sigirr prevents murine lupus by suppressing the immunostimulatory effects of lupus autoantigens**
Maciej Lech, Onkar P. Kulkarni, Stephanie Pfeiffer, Emina Savarese, Anne Krug, Cecilia Garlanda, Alberto Mantovani, and Hans-Joachim Anders

1889 **Autoregulation of Th1-mediated inflammation by *twist1***
Uwe Niesner, Inka Albrecht, Marko Janke, Cornelia Doebis, Christoph Loddenkemper, Maria H. Lexberg, Katharina Eulenburg, Stephan Kreher, Juliana Koeck, Ria Baumgrass, Kerstin Bonhagen, Thomas Kamradt, Philipp Enghard, Jens Y. Humrich, Sascha Rutz, Ulf Schulze-Topphoff, Orhan Aktas, Sina Bartfeld, Helena Radbruch, Ahmed N. Hegazy, Max Löhning, Daniel C. Baumgart, Rainer Duchmann, Martin Rudwaleit, Thomas Häupl, Inna Gitelman, Veit Krenn, Joachim Gruen, Jochen Sieper, Martin Zeitz, Bertram Wiedenmann, Frauke Zipp, Alf Hamann, Michal Janitz, Alexander Scheffold, Gerd R. Burmester, Hyun D. Chang, and Andreas Radbruch
See news item on page 1717

1903 **Human interleukin 17–producing cells originate from a CD161$^+$CD4$^+$ T cell precursor**
Lorenzo Cosmi, Raffaele De Palma, Veronica Santarlasci, Laura Maggi, Manuela Capone, Francesca Frosali, Gabriella Rodolico, Valentina Querci, Gianfranco Abbate, Roberta Angeli, Liberato Berrino, Massimiliano Fambrini, Marzia Caproni, Francesco Tonelli, Elena Lazzeri, Paola Parronchi, Francesco Liotta, Enrico Maggi, Sergio Romagnani, and Francesco Annunziato

1917 **Metalloproteinase regulation improves in vitro generation of efficacious platelets from mouse embryonic stem cells**
Hidekazu Nishikii, Koji Eto, Noriko Tamura, Koichi Hattori, Beate Heissig, Taisuke Kanaji, Akira Sawaguchi, Shinya Goto, Jerry Ware, and Hiromitsu Nakauchi
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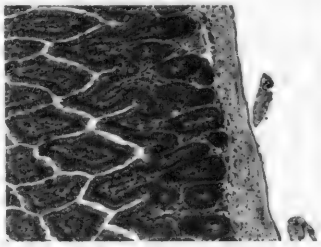
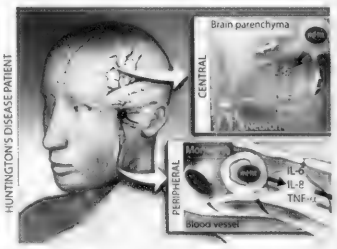


Intestinal Paneth cells (blue) produce IL-17, which drives TNF-induced systemic inflammation.
See page 1755

CORRECTIONS

1939 **The role of the Runx transcription factors in thymocyte differentiation and in homeostasis of naive T cells**
Takeshi Egawa, Robert E. Tillman, Yoshinori Naoe, Ichiro Taniuchi, and Dan R. Littman

1941 **Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses**
Lisa C. Zaba, Irma Cardinale, Patricia Gilleaudeau, Mary Sullivan-Whalen, Mayte Suárez-Fariñas, Judilyn Fuentes-Duculan, Inna Novitskaya, Artemis Khatcherian, Mark J. Bluth, Michelle A. Lowes, and James G. Krueger



Immune activation can be detected in the brain and blood as early as 15 years before the onset of Huntington's disease.
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1944 Arginine reverses T cell defects
Ticks' evasion cocktail
Spreading tolerance by converting
Chemical makeover inhibits IL-8
Large tumors too slippery for T cells?
Hema Bashyam

PEOPLE & IDEAS

1946 Caetano Reis e Sousa: harnessing DC power
Hema Bashyam

BRIEF DEFINITIVE REPORTS

1949 AID expression levels determine the extent of *cMyc* oncogenic translocations and the incidence of B cell tumor development
Makiko Takizawa, Helena Tolarová, Zhiyu Li, Wendy Dubois, Susan Lim, Elsa Callen, Sonia Franco, Maria Mosaico, Lionel Feigenbaum, Frederick W. Alt, André Nussenzweig, Michael Potter, and Rafael Casellas

1959 Blimp-1 directly represses *Il2* and the *Il2* activator *Fos*, attenuating T cell proliferation and survival
Gislâine A. Martins, Luisa Cimmino, Jerry Liao, Erna Magnusdottir, and Kathryn Calame

1967 Stimulation of Toll-like receptor 3 and 4 induces interleukin-1β maturation by caspase-8
Jonathan Maelfait, Elisabeth Vercammen, Sophie Janssens, Peter Schotte, Mira Haegman, Stefan Magez, and Rudi Beyaert

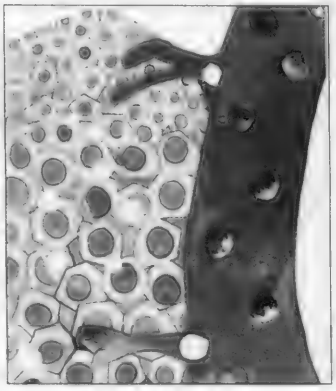
1975 $CD4^+FoxP3^+$ regulatory T cells confer infectious tolerance in a TGF-β–dependent manner
John Andersson, Dat Q. Tran, Marko Pesu, Todd S. Davidson, Heather Ramsey, John J. O'Shea, and Ethan M. Shevach
See news item on page 1944

1983 Selective miRNA disruption in T reg cells leads to uncontrolled autoimmunity
Xuyu Zhou, Lukas T. Jeker, Brian T. Fife, Shirley Zhu, Mark S. Anderson, Michael T. McManus, and Jeffrey A. Bluestone

ARTICLES

1993 Dicer-dependent microRNA pathway safeguards regulatory T cell function
Adrian Liston, Li-Fan Lu, Donal O'Carroll, Alexander Tarakhovsky, and Alexander Y. Rudensky

2005 The RNAseIII enzyme Drosha is critical in T cells for preventing lethal inflammatory disease
Mark M.W. Chong, Jeffrey P. Rasmussen, Alexander Y. Rundensky, and Dan R. Littman



ON THE COVER
Watercolor by New York artist Emilie Clark (emilie@emilieclark.com). Killer T cells (purple) fail to invade large tumors (green) due to decreased adhesion molecule expression on surrounding blood vessels. The cells that manage to reach the tumor might be suppressed by the growing population of regulatory T cells (yellow) already present. Related article by Quezada et al.
See page 2125

2019 **Ticks produce highly selective chemokine binding proteins with antiinflammatory activity**
Maud Déruaz, Achim Frauenschuh, Ana L. Alessandri, João M. Dias, Fernanda M. Coelho, Remo C. Russo, Beatriz R. Ferreira, Gerard J. Graham, Jeffrey P. Shaw, Timothy N.C. Wells, Mauro M. Teixeira, Christine A. Power, and Amanda E.I. Proudfoot
See news item on page 1944

2033 **T cell–independent development and induction of somatic hypermutation in human IgM$^+$IgD$^+$CD27$^+$ B cells**
Ferenc A. Scheeren, Maho Nagasawa, Kees Weijer, Tom Cupedo, Jörg Kirberg, Nicolas Legrand, and Hergen Spits

2043 **Repertoire-based selection into the marginal zone compartment during B cell development**
John B. Carey, Chantelle S. Moffatt-Blue, Lisa C. Watson, Amanda L. Gavin, and Ann J. Feeney

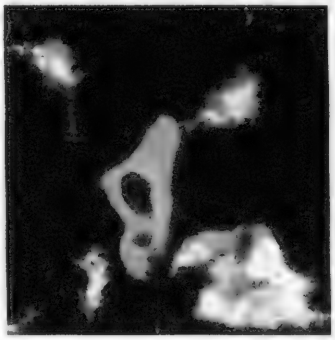
2053 **Crucial role of nitric oxide synthases system in endothelium-dependent hyperpolarization in mice**
Aya Takaki, Keiko Morikawa, Masato Tsutsui, Yoshinori Murayama, Ender Tekes, Hiroto Yamagishi, Junko Ohashi, Toyotaka Yada, Nobuyuki Yanagihara, Hiroaki Shimokawa

2065 **ADAMTS13: a new link between thrombosis and inflammation**
Anil K. Chauhan, Janka Kisucka, Alexander Brill, Meghan T. Walsh, Friedrich Scheiflinger, and Denisa D. Wagner

2075 **Role of the chemokine decoy receptor D6 in balancing inflammation, immune activation, and antimicrobial resistance in *Mycobacterium tuberculosis* infection**
Diana Di Liberto, Massimo Locati, Nadia Caccamo, Annunciata Vecchi, Serena Meraviglia, Alfredo Salerno, Guido Sireci, Manuela Nebuloni, Neus Caceres, Pere-Joan Cardona, Francesco Dieli, and Alberto Mantovani

2085 **Citrullination of CXCL8 by peptidylarginine deiminase alters receptor usage, prevents proteolysis, and dampens tissue inflammation**
Paul Proost, Tamara Loos, Anneleen Mortier, Evemie Schutyser, Mieke Gouwy, Samuel Noppen, Chris Dillen, Isabelle Ronsse, René Conings, Sofie Struyf, Ghislain Opdenakker, Prabhat C. Maudgal, and Jo Van Damme
See news item on page 1945

2099 **The transcription factor NFATc2 controls IL-6–dependent T cell activation in experimental colitis**
Benno Weigmann, Hans A. Lehr, George Yancopoulos, David Valenzuela, Andrew Murphy, Sean Stevens, Jan Schmidt, Peter R. Galle, Stefan Rose-John, and Markus F. Neurath



Patients with ulcerative colitis show increased expression of the transcription factor NFAT (red) in the gut.

A CD103$^+$ DC subset (arrows) that induces regulatory T cell differentiation is found mainly in the villi of the small intestine.

2111 **Functional skewing of the global CD8 T cell population in chronic hepatitis B virus infection**
Abhishek Das, Matthew Hoare, Nathan Davies, A. Ross Lopes, Claire Dunn, Patrick T.F. Kennedy, Graeme Alexander, Helene Finney, Alistair Lawson, Fiona J. Plunkett, Antonio Bertoletti, Arne N. Akbar, and Mala K. Maini
See news item on page 1944

2125 **Limited tumor infiltration by activated T effector cells restricts the therapeutic activity of regulatory T cell depletion against established melanoma**
Sergio A. Quezada, Karl S. Peggs, Tyler R. Simpson, Yuelei Shen, Dan R. Littman, and James P. Allison
See news item on page 1945

2139 **Small intestinal CD103$^+$ dendritic cells display unique functional properties that are conserved between mice and humans**
Elin Jaensson, Heli Uronen-Hansson, Oliver Pabst, Bertus Eksteen, Jiong Tian, Janine L. Coombes, Pia-Lena Berg, Thomas Davidsson, Fiona Powrie, Bengt Johansson-Lindbom, and William W. Agace

2151 **Toll-like receptor and IL-12 signaling control susceptibility to contact hypersensitivity**
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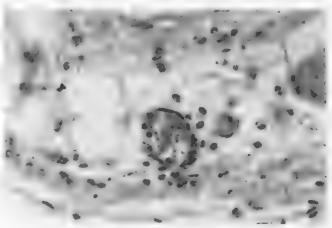
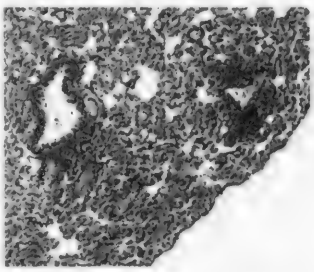
2163 **A critical role for Apc in hematopoietic stem and progenitor cell survival**
Zhijian Qian, Lina Chen, Anthony A. Fernald, Bart O. Williams, and Michelle M. Le Beau



Mice lacking the metalloprotease ADAMST13, which blocks neutrophil tethering to vessel walls, develop increased inflammation.



Deletion of the RNAase Drosha in T cells triggers lung inflammation in mice.

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2177 **TLR4-induced IFN-γ production increases TLR2 sensitivity and drives Gram-negative sepsis in mice**
Stephan Spiller, Greg Elson, Ruth Ferstl, Stefan Dreher, Thomas Mueller, Marina Freudenberg, Bruno Daubeuf, Hermann Wagner, and Carsten J. Kirschning

2179 **Tir8/Sigirr prevents murine lupus by suppressing the immunostimulatory effects of lupus autoantigens**
Maciej Lech, Onkar P. Kulkarni, Stephanie Pfeiffer, Emina Savarese, Anne Krug, Cecilia Garlanda, Alberto Mantovani, and Hans-Joachim Anders

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CAR keeps up the (heart) beat
The low-down on sugar highs
Egr-2 prevents self-reactions
Rebecca Blank & Hema Bashyam

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2184 Sabine Ehrt: Searching for mycobacterial stress points
Hema Bashyam

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2199 miR-181b negatively regulates activation-induced cytidine deaminase in B cells
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2207 Mast cell–expressed orphan receptor CCRL2 binds chemerin and is required for optimal induction of IgE-mediated passive cutaneous anaphylaxis
Brian A. Zabel, Susumu Nakae, Luis Zúñiga, Ji-Yun Kim, Takao Ohyama, Carsten Alt, Junliang Pan, Hajime Suto, Dulce Soler, Samantha J. Allen, Tracy M. Handel, Chang Ho Song, Stephen J. Galli, and Eugene C. Butcher
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2221 Human squamous cell carcinomas evade the immune response by down-regulation of vascular E-selectin and recruitment of regulatory T cells
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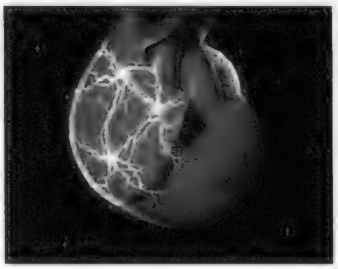

ON THE COVER
Image (provided by Bob L. Shepherd/ Photo Researchers, Inc.) shows an illustration of the electrical activity that keeps the heartbeat steady. Electrical impulses pass from the atria to the ventricles via connexin proteins, which are held in place at cell junctions by the Coxsackievirus adenovirus receptor (CAR). CAR loss disrupts the connexin connections and leads to cardiac arrythmia. Related story by Lisewski et al.
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2235 **Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein**
Pingyan Cheng, Cesar A. Corzo, Noreen Luetteke, Bin Yu, Srinivas Nagaraj, Marylin M. Bui, Myrna Ortiz, Wolfgang Nacken, Clemens Sorg, Thomas Vogl, Johannes Roth, and Dmitry I. Gabrilovich

2251 **Origin and pathogenesis of nodular lymphocyte–predominant Hodgkin lymphoma as revealed by global gene expression analysis**
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2269 **Delayed maturation of an IL-12–producing dendritic cell subset explains the early Th2 bias in neonatal immunity**
Hyun-Hee Lee, Christine M. Hoeman, John C. Hardaway, F. Betul Guloglu, Jason S. Ellis, Renu Jain, Rohit Divekar, Danielle M. Tartar, Cara L. Haymaker, and Habib Zaghouani
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2281 **GM-CSF mediates autoimmunity by enhancing IL-6–dependent Th17 cell development and survival**
Ivo Sonderegger, Giandomenica Iezzi, Reinhard Maier, Nicole Schmitz, Michael Kurrer, and Manfred Kopf

2295 **Early growth response gene 2 (Egr-2) controls the self-tolerance of T cells and prevents the development of lupuslike autoimmune disease**
Bo Zhu, Alistair L.J. Symonds, Joanne E. Martin, Dimitris Kioussis, David C. Wraith, Suling Li, and Ping Wang
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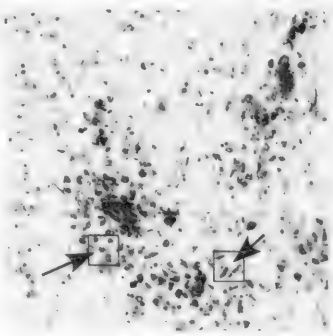
2309 **Dissecting T cell lineage relationships by cellular barcoding**
Koen Schepers, Erwin Swart, Jeroen W.J. van Heijst, Carmen Gerlach, Maria Castrucci, Daoud Sie, Mike Heimerikx, Arno Velds, Ron M. Kerkhoven, Ramon Arens, and Ton N.M. Schumacher

2319 **Ly6c$^+$ "inflammatory monocytes" are microglial precursors recruited in a pathogenic manner in West Nile virus encephalitis**
Daniel R. Getts, Rachael L. Terry, Meghann Teague Getts, Marcus Müller, Sabita Rana, Bimmi Shrestha, Jane Radford, Nico Van Rooijen, Iain L. Campbell, and Nicholas J.C. King

2339 **PSGL-1 engagement by E-selectin signals through Src kinase Fgr and ITAM adapters DAP12 and FcRγ to induce slow leukocyte rolling**
Alexander Zarbock, Clare L. Abram, Matthias Hundt, Amnon Altman, Clifford A. Lowell, and Klaus Ley



Inflammatory monocytes recruited into the brains of West Nile virus–infected mice are precursors of microglia (arrows).
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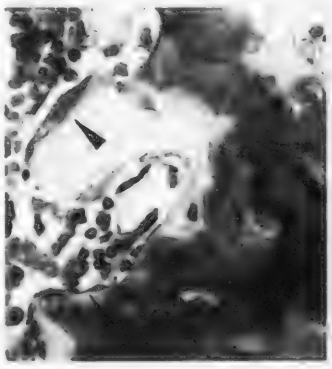

Deletion of CD45 leads to osteoclast (red) dysfunction, abnormal bone organization, and defective stem cell mobilization from the bone marrow.
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2349 **Activating transcription factor 3 is a negative regulator of allergic pulmonary inflammation**
Mark Gilchrist, William R. Henderson Jr., April E. Clark, Randi M. Simmons, Xin Ye, Kelly D. Smith, and Alan Aderem

2359 **Delayed protection by ESAT-6–specific effector CD4$^+$ T cells after airborne *M. tuberculosis* infection**
Alena M. Gallegos, Eric G. Pamer, and Michael S. Glickman

2369 **The tight junction protein CAR regulates cardiac conduction and cell–cell communication**
Ulrike Lisewski, Yu Shi, Uta Wrackmeyer, Robert Fischer, Chen Chen, Alexander Schirdewan, Rene Jüttner, Fritz Rathjen, Wolfgang Poller, Michael H. Radke, and Michael Gotthardt
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2381 **CD45 regulates retention, motility, and numbers of hematopoietic progenitors, and affects osteoclast remodeling of metaphyseal trabecules**
Shoham Shivtiel, Orit Kollet, Kfir Lapid, Amir Schajnovitz, Polina Goichberg, Alexander Kalinkovich, Elias Shezen, Melania Tesio, Neta Netzer, Isabelle Petit, Amnon Sharir, and Tsvee Lapidot

2397 **TSC–mTOR maintains quiescence and function of hematopoietic stem cells by repressing mitochondrial biogenesis and reactive oxygen species**
Chong Chen, Yu Liu, Runhua Liu, Tsuneo Ikenoue, Kun-Liang Guan, Yang Liu, and Pan Zheng

2409 **Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia**
Assam El-Osta, Daniella Brasacchio, Dachun Yao, Alessandro Pocai, Peter L. Jones, Robert G. Roeder, Mark E. Cooper, and Michael Brownlee
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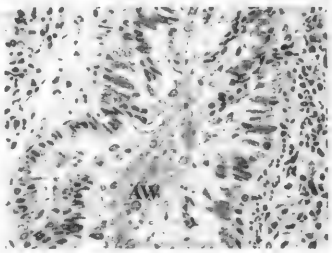
2419 **The p110δ of PI3K plays a critical role in NK cell terminal maturation and cytokine/chemokine generation**
Hailong Guo, Asanga Samarakoon, Bart Vanhaesebroeck, and Subramaniam Malarkannan

2437 **Increased IL-12 inhibits B cells' differentiation to germinal center cells and promotes differentiation to short-lived plasmablasts**
Sun Jung Kim, Michele Caton, Chuansheng Wang, Magi Khalil, Zhi-Jie Zhou, John Hardin, and Betty Diamond



Mice lacking the transcription factor ATF3 show increased airway (AW) inflammation in response to allergens.
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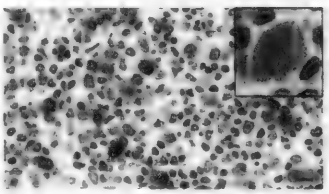

Patients with nodular lymphocyte-predominant Hodgkin's lymphoma have a high frequency of tumor cells that express activated Erk (brown).
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2449 **The RNAseIII enzyme Drosha is critical in T cells for preventing lethal inflammatory disease**
Mark M.W. Chong, Jeffrey P. Rasmussen, Alexander Y. Rudensky, and Dan R. Littman

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2457 The Death Receptor 3–TNF-like protein 1A pathway drives adverse bone pathology in inflammatory arthritis
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2465 Human PMS2 deficiency is associated with impaired immunoglobulin class switch recombination
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2473 Aquaporin-4–binding autoantibodies in patients with neuromyelitis optica impair glutamate transport by down-regulating EAAT2
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2483 Stromal mesenteric lymph node cells are essential for the generation of gut-homing T cells in vivo
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2491 Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells
Clare A. Notley, Julia J. Inglis, Saba Alzabin, Fiona E. McCann, Kay E. McNamee, and Richard O. Williams

2499 Myeloid cell differentiation arrest by miR-125b-1 in myelodysplasic syndrome and acute myeloid leukemia with the t(2;11)(p21;q23) translocation
Marina Bousquet, Cathy Quelen, Roberto Rosati, Véronique Mansat-De Mas, Roberta La Starza, Christian Bastard, Eric Lippert, Pascaline Talmant, Marina Lafage-Pochitaloff, Dominique Leroux, Carine Gervais, Franck Viguié, Jean-Luc Lai, Christine Terre, Berna Beverlo, Costantina Sambani, Anne Hagemeijer, Peter Marynen, Georges Delsol, Nicole Dastugue, Cristina Mecucci, and Pierre Brousset

ON THE COVER
Image (provided by Mehau Kulyk/Photo Researchers, Inc.) shows a colored MRI brain scan of a 10-yr-old girl suffering from multiple sclerosis (MS). In a mouse model of MS, the brain's response to interferon-γ dictates whether the spinal cord or cerebellum is the focus of disease pathology. Related story by Lees et al.
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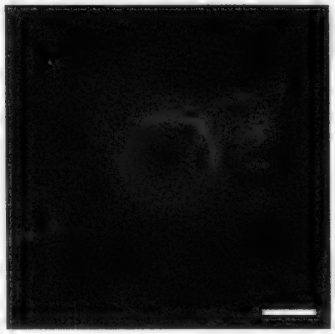
2507 **Delta-like 4 is indispensable in thymic environment specific for T cell development**
Katsuto Hozumi, Carolina Mailhos, Naoko Negishi, Ken-ichi Hirano, Takashi Yahata, Kiyoshi Ando, Saulius Zuklys, Georg A. Holländer, David T. Shima, and Sonoko Habu

2515 **Delta-like 4 is the essential, nonredundant ligand for Notch1 during thymic T cell lineage commitment**
Ute Koch, Emma Fiorini, Rui Benedito, Valerie Besseyrias, Karin Schuster-Gossler, Michel Pierres, Nancy R. Manley, Antonio Duarte, H. Robson MacDonald, and Freddy Radtke



Endocytosis of Delta-like1 (Dl1; red) is impaired in stromal cells lacking Mind bomb 1.
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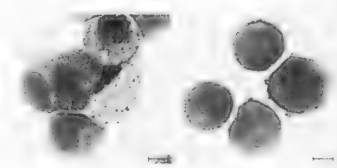
2525 **Mind bomb 1 in the lymphopoietic niches is essential for T and marginal zone B cell development**
Ran Song, Young-Woong Kim, Bon-Kyoung Koo, Hyun-Woo Jeong, Mi-Jeong Yoon, Ki-Jun Yoon, Dong-Jae Jun, Sun-Kyoung Im, Juhee Shin, Myoung-Phil Kong, Kyong-Tai Kim, Keejung Yoon, and Young-Yun Kong

2537 **Macaques vaccinated with live-attenuated SIV control replication of heterologous virus**
Matthew R. Reynolds, Andrea M. Weiler, Kim L. Weisgrau, Shari M. Piaskowski, Jessica R. Furlott, Jason T. Weinfurter, Masahiko Kaizu, Taeko Soma, Enrique J. León, Caitlin MacNair, Dan P. Leaman, Michael B. Zwick, Emma Gostick, Solomon K. Musani, David A. Price, Thomas C. Friedrich, Eva G. Rakasz, Nancy A. Wilson, Adrian B. McDermott, Rosanne Boyle, David B. Allison, Dennis R. Burton, Wayne C. Koff, and David I. Watkins

2551 **An Epstein-Barr virus–encoded microRNA targets PUMA to promote host cell survival**
Elizabeth Yee-Wai Choy, Kam-Leung Siu, Kin-Hang Kok, Raymond Wai-Ming Lung, Chi Man Tsang, Ka-Fai To, Dora Lai-Wan Kwong, Sai Wah Tsao, and Dong-Yan Jin



IL-3 and GM-CSF–induced differentiation of human CD34$^+$ cells (right) is blocked by miR-125b (left).
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2561 **CD40L$^+$ CD4$^+$ memory T cells migrate in a CD62P-dependent fashion into reactive lymph nodes and license dendritic cells for T cell priming**
Alfonso Martín-Fontecha, Dirk Baumjohann, Greta Guarda, Andrea Reboldi, Miroslav Hons, Antonio Lanzavecchia, and Federica Sallusto

2575 **Clonal deletion of thymocytes can occur in the cortex with no involvement of the medulla**
Tom M. McCaughtry, Troy A. Baldwin, Matthew S. Wilken, and Kristin A. Hogquist
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2585 **Regulation of class switch recombination and somatic mutation by AID phosphorylation**
Kevin M. McBride, Anna Gazumyan, Eileen M. Woo, Tanja A. Schwickert, Brian T. Chait, and Michel C. Nussenzweig

2595 **Tuning sensitivity to IL-4 and IL-13: differential expression of IL-4Rα, IL-13Rα1, and γc regulates relative cytokine sensitivity**
Ilkka S. Junttila, Kiyoshi Mizukami, Harold Dickensheets, Martin Meier-Schellersheim, Hidehiro Yamane, Raymond P. Donnelly, and William E. Paul

2609 **TLR3 is an endogenous sensor of tissue necrosis during acute inflammatory events**
Karen A. Cavassani, Makoto Ishii, Haitao Wen, Matthew A. Schaller, Pamela M. Lincoln, Nicholas W. Lukacs, Cory M. Hogaboam, and Steven L. Kunkel

2623 **Elevated levels of placental growth factor represent an adaptive host response in sepsis**
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2633 **Regional CNS responses to IFN-γ determine lesion localization patterns during EAE pathogenesis**
Jason R. Lees, Paul T. Golumbek, Julia Sim, Denise Dorsey, and John H. Russell
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2643 **CXCL12 (SDF-1α) suppresses ongoing experimental autoimmune encephalomyelitis by selecting antigen-specific regulatory T cells**
Moran Meiron, Yaniv Zohar, Rachel Anunu, Gizi Wildbaum, and Nathan Karin

2657 **AHI-1 interacts with BCR-ABL and modulates BCR-ABL transforming activity and imatinib response of CML stem/progenitor cells**
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2673 **MELOE-1 is a new antigen overexpressed in melanomas and involved in adoptive T cell transfer efficiency**
Yann Godet, Agnès Moreau-Aubry, Yannik Guilloux, Virginie Vignard, Amir Khammari, Brigitte Dreno, Francine Jotereau, and Nathalie Labarriere

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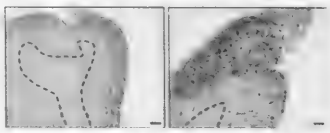
2683 **Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia**
Assam El-Osta, Daniella Brasacchio, Dachun Yao, Alessandro Pocai, Peter L. Jones, Robert G. Roeder, Mark E. Cooper, and Michael Brownlee



Delta-like4 (DL4; blue staining; right), but not DL1 (blue staining; left), is expressed in the thymic cortical epithelium.
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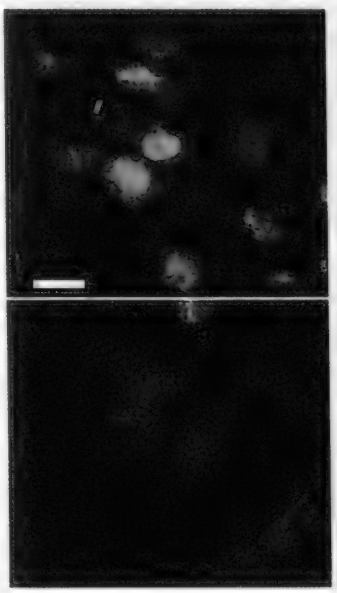

Nuclear localization of the mismatch repair protein PSM2 (top; green) is disrupted in a patient with defective class switch recombination (bottom; green).
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2703 Familial pulmonary alveolar proteinosis caused by mutations in *CSF2RA*
Takuji Suzuki, Takuro Sakagami, Bruce K. Rubin, Lawrence M. Nogee, Robert E. Wood, Sarah L. Zimmerman, Teresa Smolarek, Megan K. Dishop, Susan E. Wert, Jeffrey A. Whitsett, Gregory Grabowski, Brenna C. Carey, Carrie Stevens, Johannes C.M. van der Loo, and Bruce C. Trapnell
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2711 Pulmonary alveolar proteinosis caused by deletion of the GM-CSFRα gene in the X chromosome pseudoautosomal region 1
Margarita Martinez-Moczygemba, Minh L. Doan, Okan Elidemir, Leland L. Fan, Sau Wai Cheung, Jonathan T. Lei, James P. Moore, Ghamartaj Tavana, Lora R. Lewis, Yiming Zhu, Donna M. Muzny, Richard A. Gibbs, and David P. Huston
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2717 Activation of a dendritic cell–T cell axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells
Matthieu Perreau, Giuseppe Pantaleo, and Eric J. Kremer
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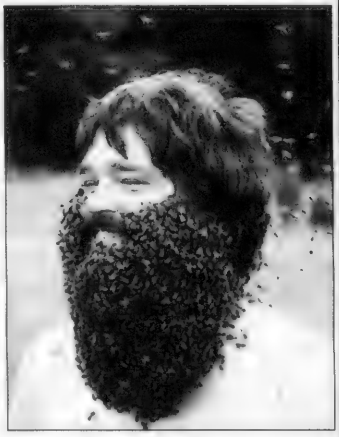
2727 A novel subset of mouse NKT cells bearing the IL-17 receptor B responds to IL-25 and contributes to airway hyperreactivity
Asuka Terashima, Hiroshi Watarai, Sayo Inoue, Etsuko Sekine, Ryusuke Nakagawa, Koji Hase, Chiaki Iwamura, Hiroshi Nakajima, Toshinori Nakayama, and Masaru Taniguchi

2735 T cell receptor contact to restricting MHC molecules is a prerequisite for peripheral interclonal T cell competition
Fabien Agenès, Jean-Pierre Dangy, and Jörg Kirberg



ON THE COVER
Image provided by Scott Camazine/ Photo Researchers, Inc. Meiler et al. show how beekeepers tolerate hundreds of stings. After multiple jabs, T cells specific for bee toxins switch from producing inflammatory cytokines to producing suppressive cytokines, thus stifling excessive inflammation.
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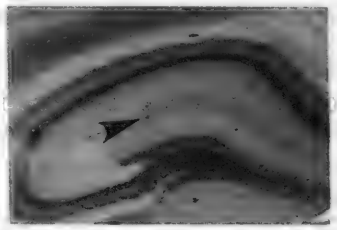
2745 **Altered kinetics of nonhomologous end joining and class switch recombination in ligase IV–deficient B cells**
Li Han and Kefei Yu

2755 **B cells drive lymphocyte activation and expansion in mice with the CD45 wedge mutation and Fas deficiency**
Vikas A. Gupta, Michelle L. Hermiston, Gail Cassafer, David I. Daikh, and Arthur Weiss



Valproic acid reduces the damaging plaques (arrow) associated with Alzheimer's disease
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2763 **Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection**
R. Brad Jones, Lishomwa C. Ndhlovu, Jason D. Barbour, Prameet M. Sheth, Aashish R. Jha, Brian R. Long, Jessica C. Wong, Malathy Satkunarajah, Marc Schweneker, Joan M. Chapman, Gabor Gyenes, Bahareh Vali, Martin D. Hyrcza, Feng Yun Yue, Colin Kovacs, Aref Sassi, Mona Loutfy, Roberta Halpenny, Desmond Persad, Gerald Spotts, Frederick M. Hecht, Tae-Wook Chun, Joseph M. McCune, Rupert Kaul, James M. Rini, Douglas F. Nixon, and Mario A. Ostrowski
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2781 **Valproic acid inhibits Aβ production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models**
Hong Qing, Guiqiong He, Philip T. T. Ly, Christopher J. Fox, Matthias Staufenbiel, Fang Cai, Zhuohua Zhang, Shengcai Wei, Xiulian Sun, Chia-Hsiung Chen, Weihui Zhou, Ke Wang, and Weihong Song
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2791 **Lipid mediators in innate immunity against tuberculosis: opposing roles of PGE_2 and LXA_4 in the induction of macrophage death**
Minjian Chen, Maziar Divangahi, Huixian Gan, Daniel S.J. Shin, Song Hong, David M. Lee, Charles N. Serhan, Samuel M. Behar, and Heinz G. Remold

2803 **Tpl2 kinase regulates T cell interferon-γ production and host resistance to *Toxoplasma gondii***
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2813 **A novel genetic strategy reveals unexpected roles of the Swi–Snf–like chromatin-remodeling BAF complex in thymocyte development**
Anant Jani, Mimi Wan, Jianmin Zhang, Kairong Cui, Jie Wu, Paula Preston-Hurlburt, Rohini Khatri, Keji Zhao, and Tian Chi

2827 **Aire controls the differentiation program of thymic epithelial cells in the medulla for the establishment of self-tolerance**
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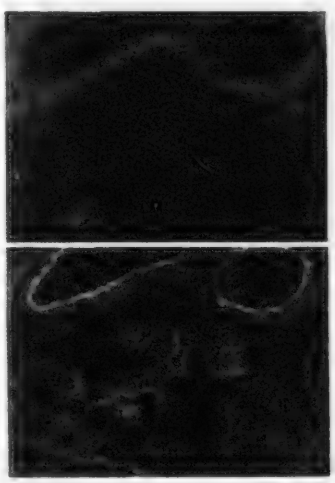

Keratin-positive salivary epithelial cells (green) express MHC class II (red) in RbAp48 transgenic mice.
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2839 **Lymph-migrating, tissue-derived dendritic cells are minor constituents within steady-state lymph nodes**
Claudia Jakubzick, Milena Bogunovic, Anthony J. Bonito, Emma L. Kuan, Miriam Merad, and Gwendalyn J. Randolph

2851 **Oncogenesis of T-ALL and nonmalignant consequences of overexpressing intracellular NOTCH1**
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2873 **ICOS-dependent extrafollicular helper T cells elicit IgG production via IL-21 in systemic autoimmunity**
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2899 **A point mutation in the murine *Hem1* gene reveals an essential role for Hematopoietic Protein 1 in lymphopoiesis and innate immunity**
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2915 **Expression of the retinoblastoma protein RbAp48 in exocrine glands leads to Sjögren's syndrome–like autoimmune exocrinopathy**
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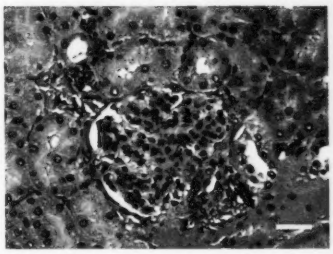
2929 **VE-PTP maintains the endothelial barrier via plakoglobin and becomes dissociated from VE-cadherin by leukocytes and by VEGF**
Astrid F. Nottebaum, Giuseppe Cagna, Mark Winderlich, Alexander C. Gamp, Ruth Linnepe, Christian Polaschegg, Kristina Filippova, Ruth Lyck, Britta Engelhardt, Olena Kamenyeva, Maria Gabriele Bixel, Stefan Butz, and Dietmar Vestweber



Renal glomeruli from Hem1$^{-/-}$ mice show histological features consistent with membranoproliferative glomerulopathy.
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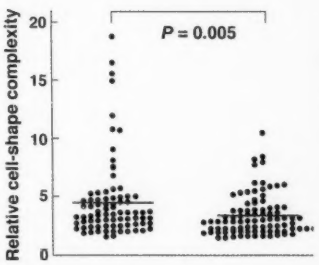

mTECs lacking functional Aire protein (right) show morphological changes compared to Aire-sufficient cells (left).
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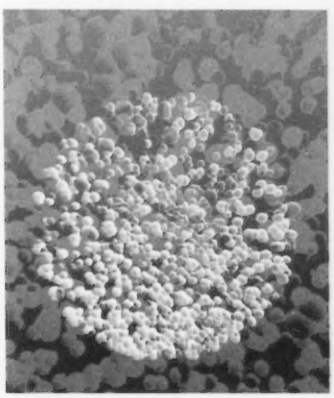

ON THE COVER
Image by New York artist Joshua Graver (JGraphicG@gmail.com) based on three-dimensional models of cell migration. These simulations predict how chemokine concentrations alter the movement of B cells in germinal centers. Related article by Figge et al.
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3007 **Induction of inflammatory and immune responses by HMGB1–nucleosome complexes: implications for the pathogenesis of SLE**
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3041 **Dendritic cells and B cells maximize mucosal Th1 memory response to herpes simplex virus**
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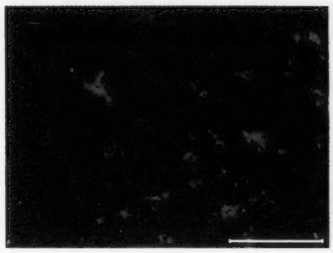

Vaginal dendritic cells (green) and B cells are required to activate protective memory CD4⁺ cells during HSV infection.
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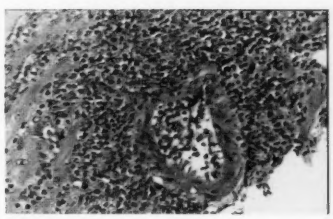

T-bet deficiency accelerates vascular inflammation and heart transplant rejection.
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3119 **Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses**
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3159 **MyD88-dependent, superoxide-initiated inflammation is necessary for flow-mediated inward remodeling of conduit arteries**
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3173 **Control of the adaptive response of the heart to stress via the Notch1 receptor pathway**
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3187 **Positive regulation of plasmacytoid dendritic cell function via Ly49Q recognition of class I MHC**
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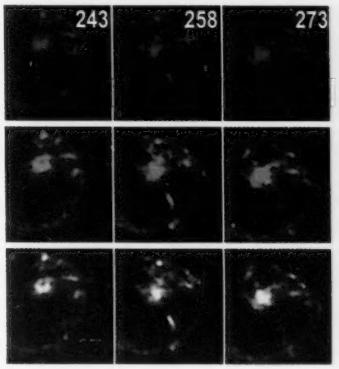
3201 **An essential role for the MAL protein in targeting Lck to the plasma membrane of human T lymphocytes**
Olga Antón, Alicia Batista, Jaime Millán, Laura Andrés-Delgado, Rosa Puertollano, Isabel Correas, and Miguel A. Alonso

CORRECTIONS

3215 **Altered kinetics of nonhomologous end joining and class switch recombination in ligase IV–deficient B cells**
Li Han and Kefei Yu



Lck (red) hitches a ride to the plasma membrane with MAL (green).
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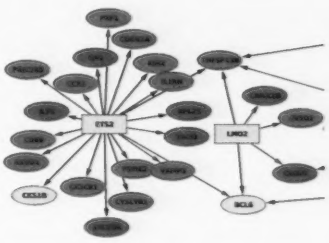

Transcriptional network of differentially expressed genes after yellow fever vaccination.
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